Attorney Docket 2000-0702/ORI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re App: Brian Hawtin Art Unit: 1619
Serial No: 09/701,140 Exam: Lauren Q Wells
Filed: November 21, 2000
For: Formulation

DECLARATION OF ALAN EDWARDS

The Commissioner of Patents and Trademarks

Washington, D.C. 20231

Sir:

I, Alan Edwards, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and a resident of Newport, Isle of Wight, UK, residing at Hanover House, Brook, and involved in the clinical evaluation of the invention described in the above-identified application for United States Letters Patent;

2. That I am presently employed by Vectis Allergy Limited where I hold the title of Medical Director, a position which I have held for 7 years, it being in the business of consultancy services to the pharmaceutical industry. Prior to that I was employed by Fisons Plc from 1974 to 1995.

3. That I have been engaged in the development and assessment of pharmaceutical compositions for the treatment of skin-related diseases and conditions for a period of at least about 22 years. Specifically, I have been engaged in the development and assessment of pharmaceutical compositions comprising sodium cromoglycate and related compounds, in relation to both skin-related diseases and conditions, and other diseases and conditions for 28 years. The compositions on which I have worked include compositions for injection, oral ingestion and inhalation as well as for topical administration. A copy of my *Curriculum vitae* is attached;

4. That in the course of these activities, I have personally become familiar with the problems encountered with transdermal transmission of pharmaceutically active drugs in topical treatments, and with the evaluation of such drugs in clinical trials;

5. That in the course of the prosecution of the above-identified application for United States Letter Patent, I have become familiar with the subject matter of the references cited by the examiner in the course of prosecution, including the following:

   British Patent No 2 202 145
   European Patent Application No 0 189 861 A2
   US Patent No 5,888,478
   US Patent No 5,190,917
   US Patent No 4,883,792
   US Patent No 5,939,085
   US Patent No 6,143,310

   and, have related the substance of the claimed subject matter to disclosures of these references;

6. That the subject matter of these references do not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

   The formulation described in the application by Totten et al (British Patent No 2 202 145) is not the same as the presently-claimed composition and has been shown not to be effective in clinical use.

   During the period 1983 to 1988 I was Director of Medical Affairs at the R & D Laboratories of Fisons Pharmaceuticals and was responsible for all clinical trials world wide.

   In particular I was responsible all clinical trials involving the development of the compound nedocromil sodium during that time. Although the main objective of the clinical development of the compound was the inhaled application for the treatment of asthma (as summarised in the publication Edwards and Stevens, Eur Resp J 1993;24:612), clinical trials were also carried out using nasal, ophthalmic, oral and skin applications.

   A limited number of trials using the skin application were carried out. Only one formulation was developed and used in these trials and it is the formulation described in the Totten et al. application.

   The limited number of trials carried out with this formulation failed to demonstrate any benefit in the condition chosen for evaluation, atopic dermatitis, and this is illustrated in the one trial that has been published (Van Bever & Stevens Eur J Pediatr 1989;149:74; attached.).

For example:

"*By the use of the daily symptom score, no significant difference could be detected between the two treatments* [formulations with and without nedocromil sodium]." (second paragraph of Results section).

"*After 4 weeks treatment both patients and clinician could not detect any difference between the two treatments using a five-point score. The two groups showed also the same usage of the escape treatment.*" (third paragraph of Results section).

"*In conclusion, 4% nedocromil sodium cream, applied during 4 weeks, twice daily has no advantage over placebo in the treatment of patients (older children and adults) with atopic dermatitis*" (final paragraph of Results section).

I had not previously recalled that any trials with this formulation had actually been published. Further development of this formulation was discontinued.

The details of the formulation given in the paper are consistent with the Totten *et al* formulation, as shown in the following table.

Comparison of the two Nedocromil formulations reported by Totten et al and Van Bever

	Totten et al	Van Bever
Oil phase		
	Glyceryl monostearate BP 4%	Glyceryl monostearate
	Cetostearyl alcohol BP 4%	Cetostearyl alcohol
	Liquid Paraffin BP 10% or 15%	
	Isopropyl Myristate BP 5%	
	Cremophor A6 2%	
	Cremophor A25 2%	
	Propyl Hydroxybenzoate BP 0.1%	Parabens
Aqueous phase		
	Methyl Hydroxybenzoate BP 0.1%	Parabens
	Potassium Sorbate BP 0.2%	Potassium Sorbate
	Sodium Acid Citrate BP 1.3%	Sodium Acid Citrate
	Sodium Hydroxide NP 0.08%	Sodium Hydroxide
	Active ingredient 4%	Active ingredient 4%
	Purified Water (low metal) to 100%	

I am sure that it is the same formulation, not only from the correspondence indicated in the table, but because only one formulation of nedocromil sodium was made by Fisons, the assignee of Totten *et al* and the supplier of the formulation used in Van Bever & Stevens.

Particularly in view of the failure reported in Van Bever & Stevens, if it was proposed to develop a new topical formulation of this class of compounds, there is no reason why anyone would choose to start from the formulation described in Totten et al. It is not in any way obvious to start from this formulation, amongst the numerous formulations that have been proposed, still less to start from the Totten et al formulation and add an amphoteric surfactant. It may appear easy after the event to rationalise why a particular formulation is successful, but beforehand there is a vast array of possibilities (both starting points and modifications) to choose from.
In contrast to the failure reported by Van Bever & Stevens, the present formulation has been used with benefit by patients, as I set out in my previous Declaration. I have also attached an updated "named patients" table, indicating further patients in which the composition has been of benefit. Despite the similarities noted by the examiner between the formulation used by Van Bever & Stevens and described by Totten *et al*, and that of the present invention, the results achieved with the present formulation are vastly superior to those achieved with the Totten *et al* formulation.

I therefore believe that the present formulation satisfies a long-felt need. It is clear from the references cited in my previous Declaration, particularly in section 6, as well as reference provided to and cited by the examiner, that topical formulations for sodium cromoglycate and nedocromil sodium have been investigated since at least 1977; yet no product has yet been marketed, despite the investigations and the unsatisfactory nature of marketed treatments, such as those for atopic dermatitis. The references that I cited in my Declaration are only examples of many more documents over a period of many years which have investigated possible topical vehicles for sodium cromoglycate and nedocromil sodium, without yielding a marketed product.

7. That based upon my education and experience, I am fully confident that the Totten *et al* reference (GB 2 202 145) reference, the Motoaki *et al* (EP 0 189 861) reference, the Maurin (US 5,888,478) reference, the Sang *et al* (US 6,143,310) reference and the Jacobs *et al* (US 5,939,085) reference whether taken alone or in combination, fail to teach or suggest

the unexpected beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

8. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosures available in the references being relied upon by examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 29th August, 2003

Alan M Edwards. MB BChir